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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/771,425	01/26/2001	Xaveer Van Ostade	4644US	8053

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EXAMINER	
LI, RUIXIANG	

ART UNIT	PAPER NUMBER
1646	9

DATE MAILED: 05/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/771,425	Applicant(s) OSTADE ET AL.	
	Examiner Ruixiang Li	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14-19 and 21-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14-19 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 January 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, Claims 1-11 and 14-19, in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Applicant's amendment in Paper NO: 8 has been entered in full. Claims 12, 13, and 20 have been canceled. New claims 21-23 have been added. Claims 1-11, 14-19, and 21-23 are pending and under consideration.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority based on an application, EPO98202528.0, filed on 07/28/1998. It is noted, however, that applicant has not filed a certified copy of the application as required by 35 U.S.C. 119(b).

Objections to Drawings

4. The drawings, Figs. 4-6, are objected to because the label "0" for the right column in each figure is confusing. The data expressed in the column appears to be a negative control and thus should be labeled as such. In addition, there is a number "5" below Fig. 4, which obviously should not be there. Correction is required.

A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Rejections—35 USC § 112, 2nd paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 11 and 15-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11 and 15-19 are indefinite because the steps recited by the methods do not necessarily achieve the goal set forth in the claim preamble.

In addition, Claims 11 and 15-19 are indefinite because it is unclear what "a series of compounds" or "each element of said series of compounds" means.

Claim Rejections—35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-6, 14, and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muthukumaran et al. (*IDS, J. Biol. Chem.* 272:4993-4999, 1997) in view of Trueheart et al. (*IDS*, WO 98/13513, April 2, 1998).

Muthukumaran et al. teach expression of chimeric erythropoietin-interferon γ receptors in CHO-B7 and CHO-16-9 cells (See, e.g., Abstract; page, 4994, right column, 6th and 7th paragraphs). The cytoplasmic part of the chimeric receptor is a cytoplasmic part of interferon γ receptor. In response to activation by EPO which was exogenously added to cells, the chimeric receptor formed homodimers or heterodimers (Fig. 8) and the cells expressing the chimeric receptor exhibited enahnced class I MHC antigen expression (Fig. 4).

Muthukumaran et al. fail to teach a second recombinant gene encoding a compound the expression of which creates an autocrine or anti-autocrinic loop.

Trueheart et al. teach expression of a large number of polypeptides in a library in the cell to identify those polypeptides that agonize or antagonize receptor bioacitivity, creating an autocrine system (page 3, last paragraph; page 51). Trueheart et al. also teach expression systems (expression vectors, promoters, etc.) used for production of polypeptides in a cDNA library (See, page 22, expression systems)

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made, as a matter of choice, instead of exogenous addition of a test compound to cells, to use a second gene encoding a compound taught by Trueheart et al. so that a compound can be expressed and an autocrine or

anti-autocrine loop can be created in cells taught by Muthukumaran et al. with a reasonable expectation of success. One would have been motivated to do so because endogenous expression of polypeptides in a cDNA library allows rapid screening of large numbers of polypeptides as taught by Trueheart et al. (page 3, last paragraph).

9. Claims 7, 8, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muthukumaran et al. in view of Trueheart et al. as applied to claims 1-6, 14, and 21-23 above, and further in view of Pellegrini et al. (*IDS, Molecular and Cellular Biology* 9:4605-4612, 1989).

Muthukumaran et al. teach expression of a chimeric receptor in cells and Trueheart et al. teach expression of polypeptides in a cDNA library as applied to claims 1-6 and 14 above. Neither Muthukumaran et al. nor Trueheart et al. teach a reporter system comprising *E. coli* xanthineguanine phosphoribosyl transferase (*gpt*) under control of a 6-16 promoter and use of 2fTGH cell as the host cells for expression of the chimeric receptors.

Pellegrini et al. teach the use of *gpt* as a reporter (marker) which is placed under control of a 6-16 promoter in 2fTGH cells (Abstract; page 4605, right column, 1st paragraph; Fig. 1).

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to construct the reporter system as taught by Pellegrini et al. and to express the chimeric receptors in 2fTGH cells with a reasonable expectation of success. One would have been motivated to do so

because the 6-16 promoter can be fused to a variety of different genes and are tightly regulated by interferon, as shown by Pellegrini et al, in the *gpt* gene in 2fTGH cells (page 4610, 1st paragraph of Discussion).

10. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Muthukumaran et al. in view of Trueheart et al. as applied to claims 1-6, 14, and 21-23 above, and further in view of Mizushima et al. (Nucleic Acids Research, 18:5322, 1990).

Muthukumaran et al. teach expression of a chimeric receptor in cells and Trueheart et al. teach expression of polypeptides in a cDNA library as applied to claims 1-6, 14, and 21-23 above. Neither Muthukumaran et al. nor Trueheart et al. teach the second recombinant gene inserted after an Sra or HEF1a promoter.

Mizushima et al. teach a mammalian expression vector containing HEF1a promoter.

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to insert the second recombinant gene after the HEF1a promoter with a reasonable expectation of success. One would have been motivated to do so because the HEF1a promoter stimulates very efficiently the in vivo transcription, as taught by Mizushima et al.

11. Claims 11 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart et al. in view of Muthukumaran et al.

Trueheart et al. teach a method for screening and identifying pharmaceutically effective compounds that specifically interact with and modulate the activity of a

receptor. The method enables rapid screening of large numbers of compounds to identify those that act as an agonist or antagonist (inhibitor) to the bioactivity of the receptor (See abstract). The method enables rapid screening of large numbers of polypeptides in a library expressed in the cell in order to identify those polypeptides which create an autocrine system (page 3, last paragraph). The autocrine assay is characterized by the use of a library of recombinant cells, each cell of which includes a target receptor protein whose signal transduction activity can be modulated by interaction with an extracellular signal, the transduction activity being able to generate a detectable signal, and an expressible recombinant gene encoding an exogenous test polypeptide from a polypeptide library (page 3, last paragraph). The specific examples refer to activation of the pherome pathway in yeast by heterologous receptors, however, it is stated that other cells (including eukaryotic cells) can be used as host cells (see page 2, last paragraph or page 20). Trueheart et al. also teach the use of several target receptors such as cytokine receptors (page 26), receptor tyrosine kinases (page 30), and G-protein coupled receptors (page 32). Trueheart et al. further teach use of the method for identifying ligands for an orphan receptor (page 9, 3rd paragraph).

However, Trueheart et al. fails to teach the use of a eukaryotic cell comprising a recombinant gene encoding a chimeric receptor.

Muthukumaran et al. teach expression of chimeric erythropoietin-interferon γ receptors in CHO-B7 and CHO-16-9 cells. The cytoplasmic part of the chimeric

receptor is a cytoplasmic part of interferon γ receptor (See, e.g., Abstract; page, 4994, right column, 6th and 7th paragraphs).

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to use the eukaryotic cell comprising a recombinant gene encoding chimeric erythropoietin-interferon γ receptors taught by Muthukumaran et al. in the method of Trueheart et al. with a reasonable expectation of success. One would have been motivated to do so because the use of a chimeric receptor has the advantage that the cytoplasmic part, for example, the interferon receptor cytoplasmic tail, is sufficient for signal transduction which is required for reporter activation, independent of the ligand-binding specificity of the chimeric recpetor.

12. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart et al. in view of Muthukumaran et al. as applied to claims 11 and 15-18 above, and further in view of Watowich et al. (*Proc. Natl. Acad. Sci. USA* 89:2140-2144, 1992).

Trueheart et al. teach a method for screening and identifying pharmaceutically effective compounds that specifically interact with and modulate the activity of a receptor, as well as for identifying ligands for an orphan receptor. Muthukumaran et al. teach expression of chimeric erythropoietin-interferon γ receptors in CHO-B7 and CHO-16-9 cells. Neither Trueheart et al. nor Muthukumaran et al. teach the use of orphan receptors that are mutated or genetically modified to a form that constitutively initiates the signaling pathway.

Watowich et al. teach a constitutively active form of erythropoietin receptor resulted from Arg→Cys mutation in the extracellular domain.

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to include a chimeric receptor comprising a constitutively active form of erythropoietin receptor taught by Watowich et al. in the method taught by Trueheart et al. and Muthukumaran with a reasonable expectation of success. One would have been motivated to do so because a constitutively active form of a chimeric receptor can be used to distinguish whether a compound (e.g., an antagonist or an inhibitor) interferes with the binding of a ligand to the receptor or with the intracellular signal transduction pathway and thus to identify a ligand for an orphan receptor, which is well known in the art.

Claim Objection-Minor Informalities

13. Claim 8 is objected to because it appears that claim 8 is dependent from claim 7, instead of claim 6. Appropriate correction is required.

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (703) 306-0282. The examiner can normally be reached on Monday through Friday, from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

Ruixiang Li
Examiner
May 17, 2002

ELIZABETH KEMMERER
PRIMARY EXAMINER